

# Modeling the Effects of Multiple Myeloma on Kidney Function

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## Abstract

Multiple myeloma, a type of plasma cell cancer, is associated with many health challenges, including damage to the kidney by tubulointerstitial fibrosis. We develop an ordinary differential equation (ODE) model which captures the qualitative behavior of the cell populations involved. Specifically, we model the interaction between cells in the proximal tubule of the kidney and free light chains produced by the myeloma monoclonal protein.

## 1 Background

Multiple myeloma (MM) is a plasma cell cancer causing development of bone disease characterized by severe bone pain and bone fractures. Other associated health challenges include hypercalcemia, anemia, and kidney damage. The American Cancer Society estimates that in 2016, about 30,330 new multiple myeloma cases will be diagnosed and about 12,650 deaths will occur in the United States.[19] Multiple myeloma most commonly occurs in older populations; the median age at diagnosis is 70, and only 5-10% of MM patients are under 40 years old [3, 5].

Although more attention has been given to how multiple myeloma affects the bone, it is also important to study the ways multiple myeloma damages the kidney, as the patient's prognosis and expected survival time is greatly affected by how well the kidney functions. In 2000, Knudsen et al. studied the survival rate of MM patients based on renal function and found that median survival was 36 months for patients with normal renal function, 18 months for patients with moderate renal failure, and 13 months for patients with severe renal failure [11]. A more recent study involving patients who received one or more novel agents demonstrated that the median overall survival for patients with renal insufficiency (defined as creatinine  $> 2$  mg/dL) was 42 months compared with 99 months for those without renal insufficiency [6]. Although patients who achieved a renal response following therapy had improved survival rates compared to those whose renal function did not improve, the survival was still significantly lower than that of patients without renal insufficiency. Thus renal dysfunction in myeloma represents a significant clinical problem.

We present a simple mathematical model and simulation results of renal degradation due to MM that captures the main players and relationships. Our model is meant to translate some basic understanding of MM for future work on predictive and prognostic models useful for patient-specific medicine. Although there exists prior work on modeling renal physiology [7, 13] and multiple myeloma separately [1, 20], to our knowledge, there is no known prior mathematical work in modeling the process of renal tubulointerstitial fibrosis caused by multiple myeloma.

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## 2 Renal Function

In order to examine the effect of multiple myeloma on the kidney, it is necessary to consider normal renal function. Humans have two kidneys, made up of systems of tubules, called nephrons, that are the working units of the kidney. Each kidney has approximately 1 million nephrons (Figure 1). The kidneys are the body's filtering system, and help maintain the body's homeostasis, the process of keeping internal conditions relatively constant or stable. The kidneys keep substances in the human body in balance by regulation and removal of metabolic waste.

The main functions of the kidney include regulation of water and electrolyte balance, which affects arterial blood pressure. The kidneys also monitor the excretion of hormones and the blood levels of prescription drugs that affect body function, as well as regulating red blood cell production and vitamin D production. Most of the kidneys' work involves transportation of water and solutes between the blood and filtration systems in the kidney. Any substance not transported back to the blood is excreted in urine.

Renal disease in multiple myeloma patients is usually present as proteinuria (excess serum proteins in the urine) [2, 12]. In general, kidney diseases related to multiple myeloma result from the kidneys' reduced ability to properly filter substances. There are two types of common tubular kidney damage that we will consider: proximal tubular cell injury, and cast formation. The sources of this damage are malignant plasma cells, which produce monoclonal proteins called monoclonal immunoglobulin (Ig) light chains (also called M proteins). Ig light chains are subunits of antibodies, which are produced by plasma cells to fight infection. Antibodies express one of two types of light chain: kappa light chain or lambda light chain. Monoclonal myeloma plasma cells overproduce Ig light chains. The most common cause of severe renal failure in multiple myeloma patients is tubulointerstitial pathology resulting from high circulating concentrations of monoclonal Ig light chains [2].

## 3 Proximal Tubule Cell Injury

Proximal tubule cell (PTC) injury is caused by free light chain interaction with PTCs. Free light chains can be toxic to PTCs by blocking transport of glucose, amino acids, or phosphates, activating tubulointerstitial fibrosis, and causing excess free light chain endocytosis [15]. Endocytosis is the process by which cells absorb proteins by engulfing them. It is important to note that not all monoclonal free light chains are toxic to the kidneys. It appears that toxicity depends on the structure of a particular individual's free light chains' 3D structure or protein folding [2, 9]. While high amount of light chains can be a sign of multiple myeloma, the more useful laboratory parameter is the serum kappa-lambda ratio. Normal kappa to lambda ratio is 0.26-1.65, compared to 0.37-3.1 in situations of renal impairment [10]. When the level of either kappa or lambda light chains is very high and the other is normal to very low, the ratio is considered abnormal, which suggests the presence of clonal plasma cells.

One way free light chains can be toxic to PTCs is by activating tubulointerstitial fibrosis. Tubulointerstitial fibrosis is the process initiated by the interaction between proximal tubule cells and free light chains, which activates inflammatory pathways in the kidney. Sustained inflammation causes the excess accumulation of extracellular matrix (ECM), which is eventually replaced by scar tissue [8]. ECM, which is made up of proteins and collagens, provides structural support to surrounding cells and most cells cannot survive unless they are anchored to the ECM. The scar tissue that replaces ECM is part of the formation of excess fibrous tissue that characterizes fibrosis. This process is considered to be largely irreversible, and leads to the loss of function of proximal tubule cells and end stage renal disease (ESRD).

Because tubulointerstitial fibrosis begins with the interaction between proximal tubule cells and free light chains, the main goal of treatment is to reduce light chain production by killing the malignant plasma cells [12]. Initial treatment includes chemotherapy drugs, hydration, and

in some cases the use of bisphosphonates to lower calcium levels. Also used as treatment is plasmapheresis, which involves removing the blood plasma from the body, treating it (reducing plasma concentration of light chains), and returning it to the body. This is similar to dialysis, which is used to remove waste from the blood. Both plasmapheresis and dialysis use machines to perform the kidneys' usual job of filtering the blood. Renal transplantation is usually not considered because of the poor prognosis of MM patients [12].

## 4 Flowchart

To better identify the various cell populations involved in the processes we model, we present a flowchart in Figure 2.

The increased monoclonal protein production by the abnormal myeloma cells leads to an increased level of free light chain molecules circulating in the blood. These free light chains are either endocytosed, or precipitated.

In the primary situation that our model addresses, the increased free light chain production leads to increased light chain endocytosis by proximal tubule cells via cubilin/megalin complex [12]. Cubilin and megalin are two endocytic receptors that play important roles in renal tubular clearance and reabsorption of proteins. They initiate receptor-mediated endocytosis, a process by which cells internalize molecules. This involves an inward budding of plasma membrane vesicles containing the monoclonal proteins with receptor sites specific to the molecules being internalized. This increased light chain endocytosis activates NF- $\kappa$  B and MAPk in the proximal tubule cells. NF- $\kappa$  B is a protein complex involved in regulating the immune system's response to inflammation, and is responsible for cytokine production. Mitogen-activated protein kinases (MAPk) direct the cellular response to mitogens and proinflammatory cytokines, which are small proteins important in cell-signaling.

The activation of NF- $\kappa$  B and MAPk initiates the production of several different types of cytokines and growth factors by the proximal tubule cells: IL-6, CCL2, IL-8 and TGF- $\beta$ . IL-6 is secreted by T-cells and macrophages to stimulate immune response, and acts as a proinflammatory cytokine. IL-8 is produced by macrophages and epithelial cells. CCL2 recruits memory T-cells and dendritic cells to inflammation sites. TGF- $\beta$  is a protein that controls cell growth, apoptosis and proliferation. These cytokines and growth factors initiate proinflammatory and fibrotic pathways, and initiate Epithelial-Mesenchymal Transition (EMT), type 2. During EMT (type 2), polarized epithelial cells (such as those that line the kidney tubules, in our case, proximal tubule cells) change to assume mesenchymal cell characteristics. This allows these cells increased migratory ability (to migrate to an infection site), increased resistance to apoptosis, and increased production of ECM material. This all plays a part in renal interstitial fibrosis, the sustained inflammation in proximal tubule epithelial cells. Fibrosis causes a disruption in the normal genesis and breakdown cycle of ECM, which leads to excessive ECM accumulation [14]. Eventually, scar tissue replaces ECM accumulation, and causes loss of function of PTCs. Ultimately, end-stage renal failure can develop.

In the secondary situation in our flowchart, non-endocytosed free light chains precipitate, forming solids called tubular casts within the kidney tubules. These casts are formed by the reaction of Ig light chains with Tamm-Horsfall protein. The casts partially or totally block the kidney tubules, which increases intraluminal pressure, reduces GFR (the sum of filtration rates of functioning nephrons), blood flow, and tubular clearance of the light chains, which increases serum light chain levels (an un-ending cycle). Unless the casts are removed, the result is permanent nephron loss.

Current kidney physiology modeling focuses on modeling chemical exchange between compartments in the kidney, and on modeling glomerular filtration rate (GFR). GFR depends on age, sex, body size, and age, and gives a good indication of how well the kidney is functioning and filtering substances in the body. To our knowledge, there is no known prior mathemati-

cal work in modeling the above process of renal tubulointerstitial fibrosis caused by multiple myeloma.

## 5 Model

Our model is a system of ordinary differential equations (ODEs) that incorporates free light chain, proximal tubule cell, fibroblast, and myeloma tumor cell populations. Based on interactions between cell populations, our model is described verbally by

$$\begin{aligned}
\text{Change in PTCs} &= + \text{natural PTC production} \\
&- \text{natural PTC death (apoptosis)} \\
&- \text{PTCs that transition via EMT to fibroblasts} \\
&- \text{PTC death due to renal interstitial fibrosis} \\
\text{Change in FLCs} &= + \text{tumor load} \\
&- \text{natural removal of light chains} \\
\text{Change in Fibroblasts} &= + \text{PTCs that transition via EMT to fibroblasts} \\
&- \text{natural fibroblast death (apoptosis)} \\
\text{Change in Tumor} &= \text{Tumor growth using Gompertz model}
\end{aligned}$$

We chose to use the Gompertz model to model the growth of the myeloma tumor. The Gompertz model was originally developed in 1825, and first proposed as a tumor growth model in 1963 [4, 16]. It is similar to an exponential growth model, but assumes a time-dependent growth rate. The Gompertz curve is sigmoidal, and reaches an asymptote as time goes on (suggesting a carrying capacity for tumor load).

The verbal description of our model is defined mathematically using the following dependent variables:

- $P(t)$  is the population of proximal tubule cells at time  $t$
- $L(t)$  is the amount of free light chains at time  $t$
- $T(t)$  is the tumor density at time  $t$
- $F(t)$  is the population of fibroblasts at time  $t$

Our system of differential equations representing these populations is

$$\frac{d}{dt}P(t) = \underbrace{\beta_P \left(1 - \frac{L}{L_S}\right)_+^{g_1} P^{g_2}}_{(1)} - \underbrace{\mu_P P}_{(2)} - \underbrace{\gamma_F L^{g_3} P^{g_4}}_{(3)}, \quad (1)$$

$$\frac{d}{dt}L(t) = \underbrace{\gamma_L T^{g_5} L^{g_6}}_{(4)} - \underbrace{\mu_L L}_{(5)}, \quad (2)$$

$$\frac{d}{dt}T(t) = \gamma_T T \log\left(\frac{L_T}{T}\right), \quad (3)$$

$$\frac{d}{dt}F(t) = \underbrace{\gamma_F L^{g_3} P^{g_4}}_{(6)} - \underbrace{\mu_F F}_{(7)}. \quad (4)$$

We define

$$(x)_+ = \begin{cases} x, & \text{if } x \geq 0, \\ 0, & \text{if } x < 0. \end{cases}$$

The use of this function ensures that the first term in (1), the inhibited proliferation rate of the PTC population, is always non-negative. The processes each term represents are as follows:

- ① represents the inhibited proliferation rate of the proximal tubule cells. The PTC proliferation rate is  $\beta_P$ ,  $L_S$  is the FLC saturation constant, and  $g_1, g_2$  are exponents. This term is always non-negative.
- ② represents natural death of proximal tubule cells. The PTC apoptosis rate is  $\mu_P$ .
- ③ represents the loss of proximal tubule cells due to EMT. The fibroblast growth constant is  $\gamma_F$ . As the number of fibroblasts increases, more PTCs undergo EMT. Here,  $g_3$  and  $g_4$  are exponents.
- ④ represents growth in the number of circulating free light chains based on tumor load. The free light chain growth constant is  $\gamma_L$  and  $g_5, g_6$  are exponents.
- ⑤ represents natural removal and production of free light chains. Natural production rate is relatively small, so  $\mu_L$  is a constant that incorporates both natural production and removal rates.
- ⑥ represents growth in number of fibroblasts due to EMT. Note that this is the same term as ① but is a source of loss for PTCs and source of growth for fibroblast population.
- ⑦ represents natural death of the fibroblast population, where  $\mu_F$  is the fibroblast natural apoptosis rate.

Our model makes use of the functionality of S-systems, which are based on power functions. S-systems are made up of equations of the form

$$\frac{dX_i}{dt} = \sum_k \alpha_k \prod_j X_j^{g_{ij}} - \sum_k \beta_k \prod_j X_j^{h_{ij}}$$

Power functions, as investigated by Voit and Savageau, have been shown to be a reasonable approximation for many biological systems. They have several properties that make them useful for modeling the complex nonlinear systems found in biology, such as the system we consider here [17, 18].

The parameters for the Gompertz model ( $\gamma_T, L_T$ ) are scaled to a dimensionless model, e.g. maximum tumor load is set to be 100. The parameter values were taken from [1]. All other parameters were obtained for the model using heuristic parameter estimation to a generic response. The model is a foundation for incorporating clinical data into a quantitative predictive system, which remains future work. The parameters used to obtain the results in this letter are listed in Table 1.

Figure 3 shows computational results generated using Matlab `ode15s`, with initial conditions  $P = 400$ ,  $L = 90$ ,  $T = 1$ , and  $F = 10$ . These results are consistent with the biology described in Figure 2: as the tumor cell population grows, the free light chain population increases, the proximal tubule cell population begins to decrease and the fibroblast population increases.

## 6 Discussion

We have developed a mathematical model for the major cell populations involved in proximal tubule cell injury due to free light chains produced by myeloma cancer cells. The system of ordinary differential equations captures the qualitative behavior of the cell populations based on a biological understanding of the process taking place inside the kidneys. This model is an initial effort. Next steps include parameterization utilizing relevant markers of renal function

and myeloma burden from patients suffering from this disease. The long-term goal is to be able to calibrate a mathematical model with a specific patient's data, and then validate the model predictions against actual patient outcomes. This type of modeling could be used to predict the likelihood of renal function recovery following myeloma therapy for those patients presenting in renal failure. Even for patients without overt signs of renal failure it has been assumed that upon diagnosis of myeloma, some degree of renal injury has already been sustained. These modeling efforts could lead to a better understanding of this sub-clinical damage and therefore have an impact on clinical strategies which could be employed to ensure optimal renal function. Success would provide clinicians with a valuable tool with genuine prognostic and predictive capabilities.

## References

- [1] Bruce P Ayati, Claire M Edwards, Glenn F Webb, and John P Wiksw. A mathematical model of bone remodeling dynamics for normal bone cell populations and myeloma bone disease. *Biol Direct.*, 5(1):28–45, 2010.
- [2] Vecihi Batuman. Proximal tubular injury in myeloma. *Contrib Nephrol.*, 153:87–104, 2007.
- [3] Brian G M Durie. Patient Handbook. URL <http://myeloma.org/pdfs/PHB.pdf>.
- [4] Philip Gerlee. The model muddle: in search of tumour growth laws. *Cancer Res.*, 73(8):2407–11, Apr 2013.
- [5] Morie A Gertz and S. Vincent. Rajkumar, editors. *Multiple Myeloma, Diagnosis and Treatment*. Springer, New York, 2014.
- [6] W I Gonsalves, N Leung, S V Rajkumar, A Dispenzieri, M Q Lacy, S R Hayman, F K Buadi, D Dingli, P Kapoor, R S Go, Y Lin, S J Russell, J A Lust, S Zeldenrust, R A Kyle, M A Gertz, and S K Kumar. Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. *Blood Cancer J.*, 5(3):e296, Mar 2015.
- [7] W Hao, BH Rovin, and A Friedman. Mathematical model of renal interstitial fibrosis. *Proc Natl Acad Sci USA.*, 111(39):14193–8, Sep 2014.
- [8] Tim D Hewitson. Renal tubulointerstitial fibrosis: common but never simple. *Am J Physiol Renal Physiol.*, 296(6):F1239–44, Jun 2009.
- [9] Colin A Hutchison and Frank Bridoux. Renal impairment in multiple myeloma: time is of the essence. *J Clin Oncol.*, 29(11):e312–e313, Apr 2011.
- [10] Colin A Hutchison, Tim Plant, Mark Drayson, Paul Cockwell, Melpomeni Kountouri, Kolitha Basnayake, Stephen Harding, Arthur R Bradwell, and Graham Mead. Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. *BMC Nephrol.*, 9:11, 2008.
- [11] L M Knudsen, M Hjorth, and E Hippe. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur J Haematol.*, 65(3):175–81, Sep 2000.
- [12] Stephen M Korbet and Melvin M Schwartz. Multiple Myeloma. *J Am Soc Nephrol*, 17:2533–2545, 2006.
- [13] Anita T. Layton and Aurelie Edwards. *Mathematical Modeling in Renal Physiology*. Springer-Verlag, Berlin Heidelberg, 2014.
- [14] Youhua Liu. Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. *J Am Soc Nephrol.*, 15(1):1–12, Jan 2004.
- [15] P. W. Sanders. Mechanisms of Light Chain Injury along the Tubular Nephron. *J Am Soc Nephrol.*, 23(11):1777–81, Nov 2012.
- [16] E. A. Sarapata and L. G. de Pillis. A comparison and catalog of intrinsic tumor growth models. *Bull Math Biol.*, 76(8):2010–24, Aug 2014.
- [17] Michael A. Savageau. *Biochemical Systems Analysis: A Study of Function and Design in Molecular Biology*. Addison-Wesley, Reading, Mass., 1976.

- [18] Michael A. Savageau and Eberhard O. Voit. Power-law approach to modeling biological systems i. theory. *J Ferment Technol.*, 34(60):221–228, 1982.
- [19] American Cancer Society. Multiple myeloma. URL <http://www.cancer.org/cancer/multiplemyeloma/index>, 2016.
- [20] Y Wang, P Pivonka, DW Smith, and CR Dunstan. Computational modeling of interactions between multiple myeloma and the bone microenvironment. *PLoS ONE*, 6(11):e27494, 2011.



Parameter List			
FLC growth constant	$\gamma_L$	.005	1/(cells days)
FLC constant	$\mu_L$	.0005	1/days
Tumor growth constant	$\gamma_T$	.005	1/days
Fibroblast growth constant	$\gamma_F$	.004	dL/(mg days)
PTC proliferation constant	$\beta_P$	.004	1/days
FLC saturation constant	$L_S$	400	mg/dL
Maximum tumor size	$L_T$	100	maximum percentage
PTC natural apoptosis rate	$\mu_P$	.0035	1/days
Natural FLC apoptosis rate	$\mu_L$	.0005	1/days
Natural fibroblast apoptosis rate	$\mu_F$	.0004	1/days
Strength of inhibited FLC on PTC growth	$g_1$	1	dimensionless
Strength of PTC on its own growth	$g_2$	1	dimensionless
Strength of FLCs on PTC growth	$g_3$	0.3	dimensionless
Strength of PTC on its own death	$g_4$	0.2	dimensionless
Strength of T on FLC growth	$g_5$	0.5	dimensionless
Strength of FLC on its own growth	$g_6$	0.5	dimensionless

Table 1: Parameters used in the computations.

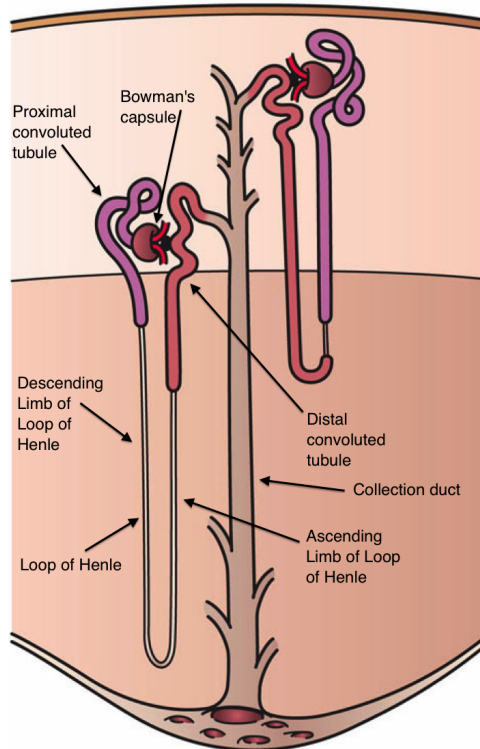


Figure 1: Nephron anatomy. The nephrons are made up of tubules, and the proximal tubule cells in our model line the proximal convoluted tubule immediately after the blood is filtered through Bowman's capsule. Image Source: <https://en.wikipedia.org/wiki/Nephron>. Reproduced without modification under Creative Commons License CC BY 3.0, <http://creativecommons.org/licenses/by/3.0/>. Artwork by Holly Fischer.

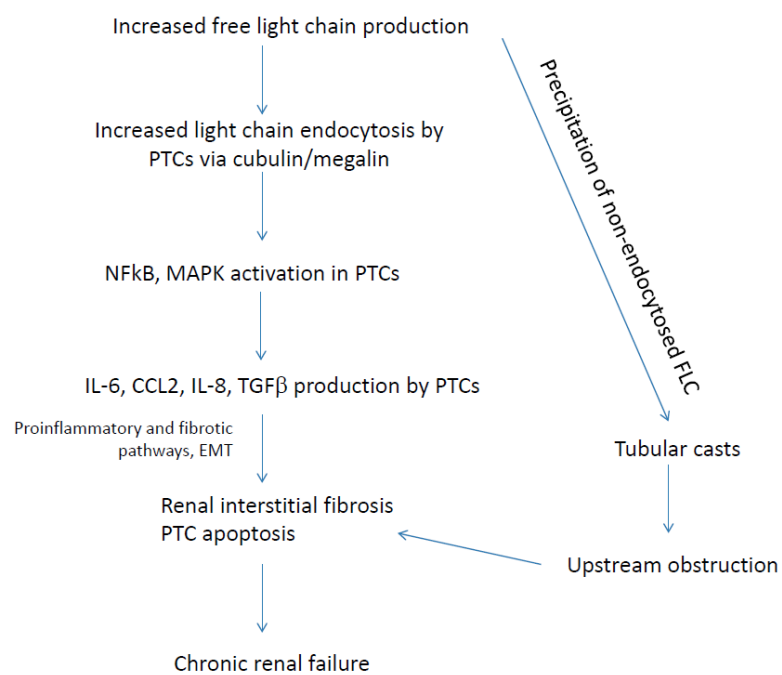


Figure 2: Light chain-mediated renal damage in multiple myeloma

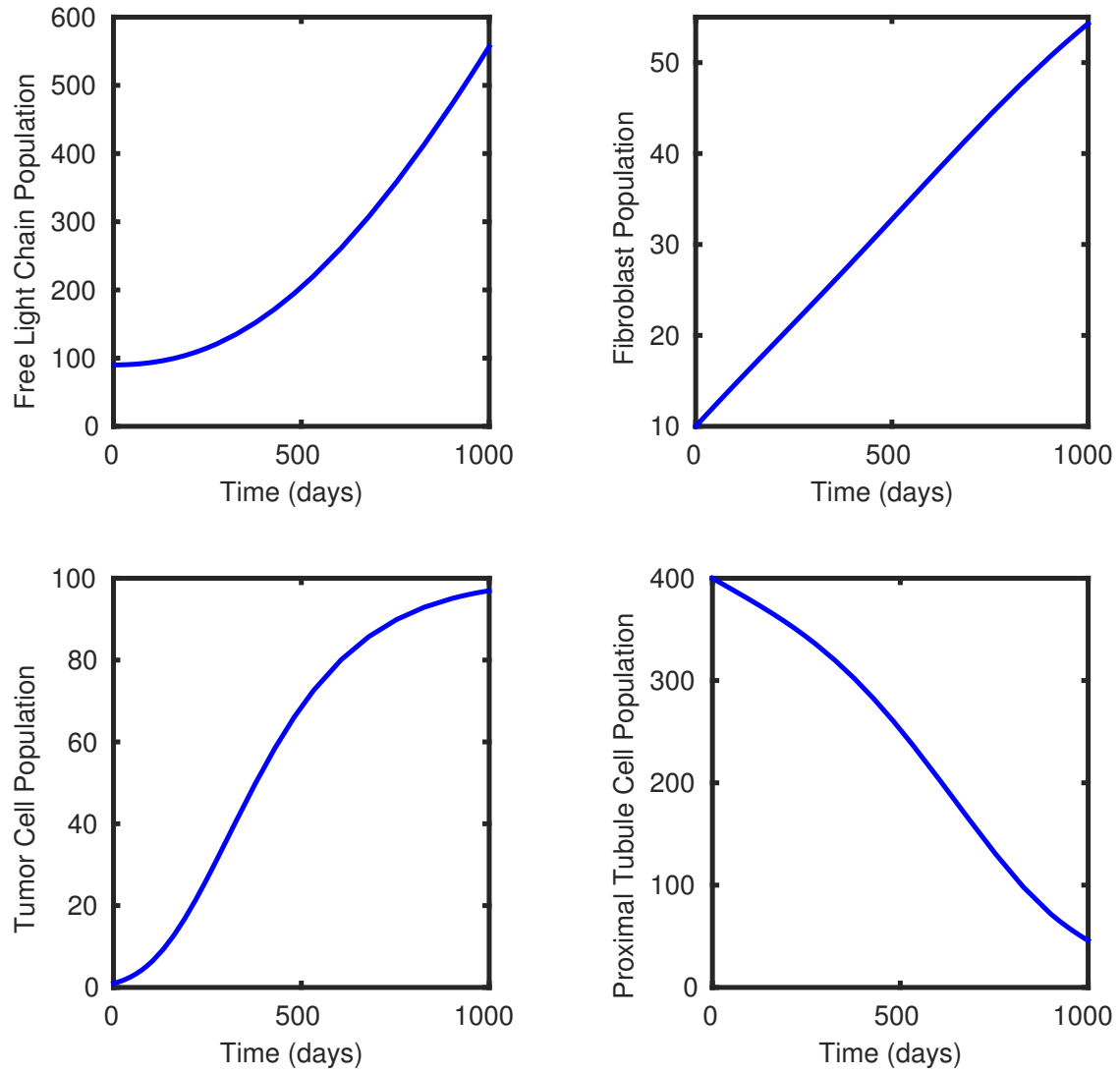


Figure 3: Computational results matching a generic renal response to multiple myeloma. Populations shown are free light chains ( $L$ ), fibroblasts ( $F$ ), tumor cells ( $T$ ), and proximal tubule cells ( $P$ ).